

## **AMENDMENTS TO THE CLAIMS**

Please amend this application as described in the Listing of Claims, which will replace all prior versions and listings of claims in the above-referenced application.

### **LISTING OF CLAIMS**

1. (Currently amended) A pharmaceutical composition comprising a biologically active agent and a mucosal delivery-enhancing effective amount of a permeabilizing peptide ~~between 4-25 amino acids in length and including one or more contiguous sequence elements~~ selected from:

a human JAM-1 peptide : VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), that effectively inhibits homotypic binding of a human JAM epithelial membrane protein;

a human claudin peptide : YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 59), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62) ), that effectively inhibits homotypic binding of a human claudin epithelial membrane protein;

and a human occludin peptide : GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42) , that effectively inhibits homotypic binding of a human claudin epithelial membrane protein,

~~wherein the permeabilizing peptide in an amount sufficient to reversibly enhances enhance mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in a mammalian subject.~~

2-9. (Cancelled)

10. (Currently amended) The pharmaceutical composition of claim 1, wherein said permeabilizing peptide ~~between 4-25 amino acids in length and includes a sequence element of~~ is a human JAM-1 peptide: VRIP (SEQ ID NO: 4).

11. (Currently amended) ~~The pharmaceutical composition of claim 1~~ A pharmaceutical composition comprising a biologically active agent of a permeabilizing peptide selected from, ~~wherein said permeabilizing peptide is between [[about]] 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:~~

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E in an amount sufficient to enhance mucosal permeation of the biologically active agent.

12. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent is selected from a small molecule drug, a peptide, a protein, and a vaccine agent.

13. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent is selected from an opiod, opiod antagonist, corticosterone, anti-inflammatory, androgen, estrogen, progestin, muscle relaxant, vasodilator, antihistamine, histamine receptor site blocking agent, antitussive, antiepileptic, anti-fungal agent, antibacterial agent, cancer therapeutic agent, antioxidant, antiarrhythmic agents, antihypertensive agent, monoclonal or polyclonal antibody, anti-sense oligonucleotide, and an RNA, DNA or viral vector comprising a gene encoding a therapeutic peptide or protein.

14. (Original) The pharmaceutical composition of claim 1, wherein said biologically active agent is selected from a therapeutic protein or peptide.

15-16. (Cancelled)

17. (Currently amended) The pharmaceutical composition of claim 1, wherein said biologically active agent and said permeabilizing peptide are administered in combination with one or more mucosal delivery-enhancing agents ~~selected from:~~

- ~~(a) an aggregation-inhibitory agent;~~
- ~~(b) a charge-modifying agent;~~
- ~~(c) a pH-control agent;~~
- ~~(d) a degradative enzyme-inhibitory agent;~~
- ~~(e) a mucolytic or mucus-clearing agent;~~
- ~~(f) a ciliostatic agent;~~

~~(g) a membrane-penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (iii) a phospholipid additive, mixed micelle, liposome, or carrier, (iv) an alcohol, (v) an enamine, (vi) an NO-donor compound, (vii) a long-chain amphipathic molecule, (viii) a small hydrophobic penetration enhancer, (ix) sodium or a salicylic acid derivative, (x) a glycerol ester of acetoacetic acid, (xi) a cyclodextrin or beta-cyclodextrin derivative, (xii) a medium-chain fatty acid, (xiii) a chelating agent, (xiv) an amino acid or salt thereof, (xv) an N-acetyl amino acid or salt thereof, (xvi) an enzyme degradative to a selected membrane component, (xvii) an inhibitor of fatty acid synthesis, or (xviii) an inhibitor of cholesterol synthesis; or (xix) any combination of the membrane-penetration-enhancing agents recited in (i) (xviii);~~

- ~~(h) a second-modulatory agent of epithelial junction physiology;~~
- ~~(i) a vasodilator agent;~~
- ~~(j) a selective transport-enhancing agent; and~~

~~(k) a stabilizing delivery vehicle, carrier, support or complex-forming species~~  
with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced mucosal delivery, wherein said one or more mucosal delivery-enhancing agents comprises any one or any combination of two or more of said mucosal delivery-enhancing agents recited in (a) (k), and wherein the formulation of said biologically active agent with said mucosal delivery-enhancing agents provides for increased in an amount sufficient to increase bioavailability of the biologically active agent delivered to a mucosal surface of a mammalian subject.

18-29. (Canceled)

30. (Original) The pharmaceutical composition of claim 1, formulated for intranasal administration.

31. (Original) The pharmaceutical composition of claim 1, formulated as an intranasal spray or powder.

32. (Currently amended) The pharmaceutical composition of claim 1, wherein said biologically active agent and said permeabilizing peptide are formulated for intranasal administration with one or more intranasal delivery-enhancing agents ~~selected from:~~

~~(a) an aggregation-inhibitory agent;~~

~~(b) a charge-modifying agent;~~

~~(c) a pH-control agent;~~

~~(d) a degradative enzyme-inhibitory agent;~~

~~(e) a mucolytic or mucus-clearing agent;~~

~~(f) a ciliostatic agent;~~

~~(g) a membrane-penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (iii) a phospholipid additive, mixed micelle, liposome, or carrier, (iv) an alcohol, (v) an enamine, (vi) an NO-donor compound, (vii) a long-chain amphipathic molecule, (viii) a small hydrophobic-penetration enhancer, (ix) sodium or a salicylic acid derivative, (x) a glycerol ester of acetoacetic acid, (xi) a cyclodextrin or beta-cyclodextrin derivative, (xii) a medium-chain fatty acid, (xiii) a chelating agent, (xiv) an amino acid or salt thereof, (xv) an N-acetyl amino acid or salt thereof, (xvi) an enzyme degradative to a selected membrane component, (xvii) an inhibitor of fatty acid synthesis, or (xviii) an inhibitor of cholesterol synthesis; or (xix) any combination of the membrane-penetration-enhancing agents recited in (i) (xviii);~~

~~(h) a second modulatory agent of epithelial junction physiology;~~

~~(i) a vasodilator agent;~~

~~(j) a selective transport-enhancing agent; and~~

~~(k) a stabilizing delivery vehicle, carrier, support or complex-forming species with which the biologically active agent is effectively combined, associated, contained,~~

~~encapsulated or bound resulting in stabilization of the active agent for enhanced mucosal delivery, wherein said one or more intranasal delivery enhancing agents comprises any one or any combination of two or more of said intranasal delivery enhancing agents recited in (a) (k), and wherein the formulation of said biologically active agent with said one or more intranasal delivery enhancing agents provides for increased in an amount sufficient to increase~~ bioavailability of the biologically active agent delivered to a nasal mucosal surface of a mammalian subject.

33. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields a peak concentration ( $C_{max}$ ) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of said subject that is 25% or greater as compared to a peak concentration of the biologically active agent following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

34. (Original) The pharmaceutical composition of claim 33, wherein said composition following mucosal administration to said subject yields a peak concentration ( $C_{max}$ ) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of said subject that is 50% or greater as compared to a peak concentration of the biologically active agent in the blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

35. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject that is 25% or greater compared to an AUC of the biologically active agent in blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

36. (Original) The pharmaceutical composition of claim 35, wherein said composition following mucosal administration to said subject yields an area under concentration curve (AUC) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject that is 50% or greater compared to an AUC of the biologically active agent in blood

plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

37. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields a time to maximal plasma concentration ( $t_{\max}$ ) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject between 0.1 to 1.0 hours.

38. (Original) The pharmaceutical composition of claim 37, wherein said composition following mucosal administration to said subject yields a time to maximal plasma concentration ( $t_{\max}$ ) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject between 0.2 to 0.5 hours.

39. (Original) The pharmaceutical composition of claim 1, wherein said composition following mucosal administration to said subject yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 10% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

40. (Original) The pharmaceutical composition of claim 39, wherein said composition following mucosal administration to said subject yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 20% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

41. (Original) The pharmaceutical composition of claim 39, wherein said composition following mucosal administration to said subject yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or fluid of the subject that is 40% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

42. (Original) The pharmaceutical composition of claim 1, wherein the biologically active agent is effective for treatment of sexual dysfunction.

43. (Original) The pharmaceutical composition of claim 42, wherein the biologically active agent is effective for treatment of male erectile sexual dysfunction.

44. (Canceled)

45. (Original) The pharmaceutical composition of claim 42, wherein the biologically active agent is a dopamine receptor agonist.

46. (Previously presented) The pharmaceutical composition of claim 42, wherein the biologically active agent is apomorphine or a pharmaceutically acceptable salt or derivative thereof.

47. (Canceled)

48. (Withdrawn) A method for treating or preventing a disease or condition in a mammalian subject amenable to treatment by therapeutic administration of a biologically active, therapeutic agent, comprising mucosally administering to said subject a pharmaceutical formulation comprising a mucosal delivery-enhancing effective amount of a permeabilizing peptide that reversibly enhances mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in the subject, wherein said peptide effectively inhibits homotypic binding of an epithelial membrane adhesive protein selected from a junctional adhesion molecule (JAM), occludin, or claudin, and coordinately administering the biologically active, therapeutic agent.

49. (Withdrawn) The method of claim 48, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence elements selected from a human JAM-1 peptide, VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), a human claudin peptide YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 53), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ

ID NO: 62), or a human occludin peptide GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42).

50. (Withdrawn) The method of claim 48, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.

51. (Withdrawn) The method of claim 48, wherein said permeabilizing peptide has a sequence selected from VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), or EDTGTYTCM (SEQ ID NO: 9).

52. (Withdrawn) The method of claim 48, wherein said mucosal administration involves delivery of said formulation to a nasal mucosal surface of said subject.

53. (Withdrawn) The method of claim 48, wherein the dopamine receptor agonist is apomorphine or a pharmaceutically acceptable salt or derivative thereof.

54. (Withdrawn) A coordinate administration method for enhanced mucosal delivery of a biologically active agent comprising:

administering to a mammalian subject an mucosally effective amount of at least one biologically active agent in a coordinate administration protocol with a mucosal delivery-enhancing effective amount of a permeabilizing peptide that reversibly enhances mucosal



epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in the subject, wherein said peptide effectively inhibits homotypic binding of an epithelial membrane adhesive protein selected from a junctional adhesion molecule (JAM), occludin, or claudin.

55. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is administered before, simultaneous with, or following coordinate administration of said permeabilizing peptide.

56. (Withdrawn) The coordinate administration method of claim 55, wherein said permeabilizing peptide is administered prior to administration of said biologically active agent by an effective pre-administration period to yield enhancement of mucosal epithelial paracellular transport.

57. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are administered essentially simultaneously in a mixture or contemporaneously applied, separate formulations.

58. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

59. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 6-15 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

60. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian JAM-1, JAM-2, or JAM-3 protein.

61. (Withdrawn) The coordinate administration method of claim 60, wherein said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid substitutions, insertions, or deletions compared to said corresponding reference sequence of the mammalian JAM-1, JAM-2, or JAM-3 protein.

62. (Withdrawn) The coordinate administration method of claim 60, wherein said permeabilizing peptide is a human JAM-1 peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of the human JAM-1 protein, said mutation(s) corresponding to a structural feature identified in a human JAM-2 or JAM-3 protein.

63. (Withdrawn) The coordinate administration method of claim 60, wherein said permeabilizing peptide is a human JAM-1, JAM-2, or JAM-3 peptide and said amino acid sequence of said permeabilizing peptide exhibits one or more amino acid mutations in comparison to a corresponding wild-type sequence of a human JAM-1, JAM-2, or JAM-3 protein, respectively, said mutation(s) corresponding to a structural feature identified in a murine, rat, or bovine JAM-1, JAM-2 or JAM-3 protein, respectively.

64. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence elements selected from a human JAM-1 peptide, VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), a human claudin peptide YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 53), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62), or a human occludin peptide GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42).

65. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide is between about 4-25 amino acids in length and includes one or more contiguous sequence motifs selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.

66. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is selected from a small molecule drug, a peptide, a protein, and a vaccine agent.

67. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is selected from an opiod, opiod antagonist, corticosterone, anti-inflammatory, androgen, estrogen, progestin, muscle relaxant, vasodilator, antihistamine, histamine receptor site blocking agent, antitussive, antiepileptic, anti-fungal agent, antibacterial agent, cancer therapeutic agent, antioxidant, antiarrhythmic agents, antihypertensive agent, monoclonal or polyclonal antibody, anti-sense oligonucleotide, and an RNA, DNA or viral vector comprising a gene encoding a therapeutic peptide or protein.

68. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is a therapeutic protein or peptide selected from tissue plasminogen activator (TPA), epidermal growth factor (EGF), fibroblast growth factor (FGF-acidic or basic), platelet derived growth factor (PDGF), transforming growth factor (TGF-alpha or beta), vasoactive intestinal peptide, tumor necrosis factor (TGF), hypothalamic releasing factors, prolactin, thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH),

parathyroid hormone (PTH), follicle stimulating hormone (FSH), luteinizing hormone releasing (LHRH), endorphins, glucagon, calcitonin, oxytocin, carbetocin, aldoetecone, enkephalins, somatostatin, somatotropin, somatomedin, gonadotrophin, estrogen, progesterone, testosterone, alpha-melanocyte stimulating hormone, non-naturally occurring opioids, lidocaine, ketoprofen, sufentanil, terbutaline, droperidol, scopolamine, gonadorelin, ciclopirox, olamine, buspirone, calcitonin, cromolyn sodium or midazolam, cyclosporin, lisinopril, captopril, delapril, cimetidine, ranitidine, famotidine, superoxide dismutase, asparaginase, arginase, arginine deaminase, adenosine deaminase ribonuclease, trypsin, chemotrypsin, papain, bombesin, substance P, vasopressin, alpha-globulins, transferrin, fibrinogen, beta-lipoproteins, beta-globulins, prothrombin, ceruloplasmin, alpha<sub>2</sub>-glycoproteins, alpha<sub>2</sub>-globulins, fetuin, alpha-lipoproteins, alpha-globulins, albumin, and prealbumin.

69. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent is a therapeutic protein or peptide effective as a hematopoietic agent, cytokine agent, anti-infective agent, anti-dementia agent, antiviral agent, anti-tumoral agent, anti-pyretic agent, analgesic agent, anti-inflammatory agent, anti-ulcer agent, anti-allergic agent, anti-depressant agent, psychotropic agent, cardiogenic agent, anti-arrhythmic agent, vasodilator agent, anti-hypertensive agent, anti-diabetic agent, anticoagulant agent, cholesterol-lowering agent, hormone agent, anti-osteoporosis agent, antibiotic agent, vaccine agent, or bacterial toxin.

70. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are administered in combination with one or more mucosal delivery-enhancing agents selected from:

- (a) an aggregation inhibitory agent;
- (b) a charge modifying agent;
- (c) a pH control agent;
- (d) a degradative enzyme inhibitory agent;
- (e) a mucolytic or mucus clearing agent;
- (f) a ciliostatic agent;

(g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (iii) a phospholipid additive, mixed micelle, liposome, or carrier, (iv) an enamine, (v) an NO donor compound, (vi) a long-chain amphipathic molecule (vii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a cyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetyl amino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x);

(h) a second modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, support or complex-forming species

with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced mucosal delivery, wherein said one or more mucosal delivery-enhancing agents comprises any one or any combination of two or more of said mucosal delivery-enhancing agents recited in (a)-(k), and wherein the formulation of said biologically active agent with said mucosal delivery-enhancing agents provides for increased bioavailability of the biologically active agent delivered to a mucosal surface of a mammalian subject.

71. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

72. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian occludin protein.

73. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

74. (Withdrawn) The coordinate administration method of claim 54, wherein said permeabilizing peptide comprises from about 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein or comprises an amino acid sequence that exhibits at least 85% amino acid identity with a corresponding reference sequence of 4-25 contiguous amino acids of an extracellular domain of a mammalian claudin protein.

75. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are administered intranasally.

76. (Withdrawn) The coordinate administration method of claim 54, wherein said biologically active agent and said permeabilizing peptide are coordinately administered or formulated in combination with one or more intranasal delivery-enhancing agents selected from:

- (a) an aggregation inhibitory agent;
- (b) a charge modifying agent;
- (c) a pH control agent;
- (d) a degradative enzyme inhibitory agent;
- (e) a mucolytic or mucus clearing agent;
- (f) a ciliostatic agent;
- (g) a membrane penetration-enhancing agent selected from (i) a surfactant, (ii) a bile salt, (iii) a phospholipid additive, mixed micelle, liposome, or carrier, (iv) an alcohol, (v) an enamine, (vi) an NO donor compound, (vii) a long-chain amphipathic molecule (viii) a small hydrophobic penetration enhancer; (viii) sodium or a salicylic acid derivative; (ix) a glycerol ester of acetoacetic acid (x) a cyclodextrin or beta-cyclodextrin derivative, (xi) a medium-chain fatty acid, (xii) a chelating agent, (xiii) an amino acid or salt thereof, (xiv) an N-acetylamino acid or salt thereof, (xv) an enzyme degradative to a selected membrane component, (ix) an inhibitor of fatty acid synthesis, or (x) an inhibitor of cholesterol synthesis; or (xi) any combination of the membrane penetration enhancing agents recited in (i)-(x);

(h) a second modulatory agent of epithelial junction physiology;

(i) a vasodilator agent;

(j) a selective transport-enhancing agent; and

(k) a stabilizing delivery vehicle, carrier, support or complex-forming species

with which the biologically active agent is effectively combined, associated, contained, encapsulated or bound resulting in stabilization of the active agent for enhanced intranasal delivery, wherein said one or more intranasal delivery-enhancing agents comprises any one or combination of two or more of said intranasal delivery-enhancing agents recited in (a)-(k), and wherein the coordinate administration or combinatorial formulation of said biologically active agent with said one or more intranasal delivery-enhancing agents provides for increased bioavailability of the biologically active agent delivered to a nasal mucosal surface of a mammalian subject.

77. (Withdrawn) The coordinate administration method of claim 54, which yields a peak concentration ( $C_{\max}$ ) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of said subject that is 25% or greater as compared to a peak concentration of the biologically active agent following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

78. (Withdrawn) The coordinate administration method of claim 54, which yields an area under concentration curve (AUC) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject that is 25% or greater compared to an AUC of the biologically active agent in blood plasma or CNS following intramuscular injection of an equivalent concentration or dose of the active agent to said subject.

79. (Withdrawn) The coordinate administration method of claim 54, which yields a time to maximal plasma concentration ( $t_{\max}$ ) of said biologically active agent in a blood plasma or cerebral spinal fluid (CNS) of the subject between 0.2 to 0.5 hours.

80. (Withdrawn) The coordinate administration method of claim 54, which yields a peak concentration of said biologically active agent in a central nervous system (CNS) tissue or

fluid of the subject that is 10% or greater compared to a peak concentration of said biologically active agent in a blood plasma of the subject.

81. (Withdrawn) The coordinate administration method of claim 54, wherein the biologically active agent is selected from interferon- $\alpha$ , interferon- $\beta$ , human growth hormone (HGH), insulin, heparin, nerve growth factor (NGF), erythropoietin (EPO), acetylcholinesterase (ACTH), amyloid peptide, beta-sheet blocking peptide, natriuretic peptide, ketoprofen, and oleamide.

82. (Currently amended) A permeabilizing peptide ~~between 4-25 amino acids in length including one or more contiguous sequence elements~~ selected from:

a human JAM-1 peptide : VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTGM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10), that effectively inhibits homotypic binding of a human JAM epithelial membrane protein;

a human claudin peptide : YAGDNIVTAQ (SEQ ID NO: 57), MTPVNARYEF (SEQ ID NO: 58), GILRDFYSPL (SEQ ID NO: 59), VPDSMKFEIG (SEQ ID NO: 60), DIYSTLLGLP (SEQ ID NO: 55), GFSGLGLWMEC (SEQ ID NO: 56), NTIIRDFYNP (SEQ ID NO: 54), VVPEAQKREM (SEQ ID NO: 63), VASGQKREMG (SEQ ID NO: 59), NIIQDFYNPL (SEQ ID NO: 61), or VPVSQKYELG (SEQ ID NO: 62) ), that effectively inhibits homotypic binding of a human claudin epithelial membrane protein;

and a human occludin peptide : GVNPTAQSS (SEQ ID NO: 33), GSLYGSQIY (SEQ ID NO: 34), AATGLYVDQ (SEQ ID NO: 32), ALCNQFYTP (SEQ ID NO: 35), or YLYHYCVVD (SEQ ID NO: 42) , that effectively inhibits homotypic binding of a human claudin epithelial membrane protein,

~~wherein the permeabilizing peptide in an amount sufficient to enhance mucosal epithelial paracellular transport by modulating epithelial junctional structure and/or physiology in a mammalian subject.~~

83-88. (Canceled)



89. (Currently amended) The permeabilizing peptide of claim 82, which is a human JAM-1, JAM-2, or JAM-3 peptide.

90. (Currently amended) The permeabilizing peptide of claim 82, which ~~includes one or more contiguous sequence elements~~ selected from a human JAM-1 peptide: VRIP (SEQ ID NO: 4), VKLSCAY (SEQ ID NO: 5), TGITFKSVT (SEQ ID NO: 6), ITAS (SEQ ID NO: 7), SVTR (SEQ ID NO: 8), EDTGTYTCM (SEQ ID NO: 9), or GFSSPRVEW (SEQ ID NO: 10).

91. (Currently amended) The permeabilizing peptide of claim 82, which ~~includes a sequence element of~~ is a human JAM-1 peptide: VRIP (SEQ ID NO: 4).

92. (Currently amended) The permeabilizing peptide of claim 82, which is ~~between about 4-25 amino acids in length and includes one or more contiguous sequence motifs~~ selected from:

VR(I,V,A)P (SEQ ID NO: 1), wherein the third position of the motif may be represented by one of the alternative amino acid residues I, V, or A;

(V,A,I)KL(S,T)CAY (SEQ ID NO: 2), wherein the first position of the motif may be represented by one of the alternative amino acid residues V, A, or I, and the fourth position of the motif may be represented by one of the alternative amino acid residues S or T; and

ED(T,S)GTY(T,R)C(M,E) (SEQ ID NO: 3), wherein the third position of the motif may be represented by one of the alternative amino acid residues T or S, the seventh position of the motif may be represented by one of the alternative amino acid residues T or R, and the ninth position of the motif may be represented by one of the alternative residues M or E.